National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 8 Highlights
Disabled American Veterans Building
807 Maine Avenue
Washington, D.C.
December 8-10, 1997

INTRODUCTION

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 7 (September 23-25, 1997) were reviewed and approved (Appendix A).

Dr. Roger Garrett reported that comments had been received on the AEGLs published in the Federal Register and that the public comment period was closed. He also stated that there had been a meeting with the National Academy of Sciences (NAS) Committee on Toxicology (COT) and that arrangements are in progress for COT review of Interim AEGL values.

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group
A report from the SOP Working Group was given by Ernest Falke. An overview of the first three chapters (Calculations of AEGL Values, Format and Content of Technical Support Documents, Development of Information and Data for Technical Support Documents [TSD]) was provided. Topics for which work is currently in progress include AEGL endpoints (e.g., types of endpoints, categorization of endpoints and their relationship to AEGL levels) and time scaling (e.g., how concentration-time relationship varies with endpoint, concentration range, or time frame; derivation of *n* and relevant statistics). Additional issues were mentioned that should also be addressed in the SOP and they include: contact and use of manufacturers' information, sharing of draft TSD with chemical manufacturers prior to the NAC/AEGL meetings, review procedures (i.e., TSD review, Federal Register comment period, COT process), and refinement of definitions (e.g., "ceiling level," "notable discomfort").

Action Item: Provide comments on SOP to Ernest Falke ASAP. He would like to have a revised SOP by 1/1/98.

Deriving AEGLs by Bench Dose Approach
Bob Benson and Bob Snyder volunteered to do this and will report their results in the next NAC meeting.

Federal Register Comments on Proposed Draft AEGLs
Roger Garrett and Rich Neimeier presented a brief overview of the public comments on the Proposed AEGLs published in the Federal Register (Vol. 62, No. 210, pp. 58840-58851). Both chemical-specific and general comments were received and provided by the Federal Register office.

They were reviewed first time during the meeting. A total of ten parties provided comments as of that date.

Richard Thomas and Ernie Falke will discuss the human equivalence adjustment for hydrazine.

A motion was made (Mark McClanahan), seconded (Loren Koller), and approved that the following AEGLs be considered as Interim AEGLs and that they be forwarded to the COT: 1,1-dimethylhydrazine, 1,2,-dimethylhydrazine, methylhydrazine, aniline, 1,2-dichloroethylene, nitric acid, fluorine, and arsine.

American Chemical Society (ACS) Presentations

Nancy Kim, George Rodgers and Robert Young presented abbreviated versions of their talks originally presented at the American Chemical Society meeting in Las Vegas (September 1997). These presentations were part of the Chemical Health and Safety Division symposium entitled "National Program for the Development and Use of Acute Exposure Guideline Levels" organized by Po-Yung Lu, Paul Tobin, and Roger Garrett. Nancy Kim spoke about the tracking of accidental releases in the state of New York and the application of AEGLs. George Rodgers presented information pertaining to sensitive populations, pertinent factors to consider in this respect for the development of AEGLs, and examples of sensitive responders. Robert Young provided an overview of the development of Technical Support Documents and some of the thought processes relevant to data evaluation and derivation of draft proposed AEGLs.

AEGL PRIORITY CHEMICALS

Phosgene, CAS No. 75-44-5

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Cheryl Bast, ORNL

Cheryl Bast provided an overview of the work on the phosgene draft AEGLs and the most recent adjustment to these values (Attachment 3). T. D. Landry (Dow Chemical), representing the Chemical Manufacturers Association (CMA) Phosgene Panel, stated that the CMA supported the values but considered the use of Haber's Rule (linear extrapolation) for 4-hour and 8-hour AEGLs to result in somewhat conservative, but appropriately protective, values (Attachment 4). Dr. Werner Diller (also representing the CMA Phosgene Panel) provided positive comments on the phosgene TSD and the AEGL endpoints (Attachment 5), but remarked that he had reservations regarding the "Not Applicable" status for AEGL-1 and the use of animal data to derive the AEGLs. He indicated that the proposed draft AEGLs were somewhat low (due to interspecies uncertainty factor application) and that they did not necessarily reflect the human experience. Discussion followed regarding the relationship between the AEGL values and the TLV, and the application of a benchmark dose approach for evaluating the data. A motion was made (Loren Koller) and seconded (George Rodgers) to accept the proposed draft AEGLs for phosgene. The motion passed (YES:23; NO:0; ABSTAIN:0; ABSENT:9) (Appendix B). The proposed AEGLs for phosgene are shown in

the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSGENE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.60 ppm (2.5 mg/m^3)	0.30 ppm (1.2 mg/m^3)	0.08 ppm (0.33 mg/m^3)	0.04 ppm (0.16 mg/m^3)	chemical pneumonia in rats (Gross et al., 1965)
AEGL-3	1.5 ppm (6.2 mg/m^3)	0.75 ppm (3.1 mg/m^3)	0.20 ppm (0.82 mg/m^3)	0.09 ppm (0.34 mg/m^3)	30-min no effect level for lethality in rats (Zwart et al., 1990)

Hydrogen Cyanide, CAS No. 74-90-8

Chemical Manager: Dr. George Rodgers, AAPCC
Author: Dr. Sylvia Talmage, ORNL

George Rodgers presented an overview of cyanide toxicology and metabolism, and briefly discussed populations at risk. Overall, the toxic response to cyanide is similar across species with sensitivity variances being due primarily to variable levels of rhodanese. The AEGL values presented in the draft TSD appeared to be consistent with occupational standards and criteria, and the available acute toxicity data for this chemical. The draft AEGLs in the TSD were derived using a total uncertainty factor of 6 (3 for intraspecies variability and 2 for interspecies variability). A discussion on the interspecies uncertainty factor followed. George Rodgers moved that the AEGL values as originally proposed in the TSD be accepted with the following modifications: change the interspecies uncertainty factor to 1 and add a modifying factor of 2. Loren Koller seconded the motion which carried (YES:24; NO:1; ABSTAIN:0; ABSENT:8) (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CYANIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	toxicity below odor threshold
AEGL-2	10 ppm (11 mg/m3)	7 ppm (7.8 mg/m3)	3.5 ppm (3.9 mg/m3)	2.5 ppm (2.8 mg/m3)	slight central nervous system depression (Purser, 1984)
AEGL-3	21 ppm (23 mg/m3)	15 ppm (17 mg/m3)	8.6 ppm (9.7 mg/m3)	6.6 ppm (7.3 mg/m3)	lethality (LC_{01}) in rats (E.I. duPont de Nemours, 1981)

Carbon Tetrachloride, CAS No. 56-23-5

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Robert Young, ORNL

Robert Young presented the data sets pertinent to derivation of AEGLs for carbon tetrachloride and the draft proposed AEGLs (Attachment 6). The draft proposed AEGL-1 and AEGL-2 values were based upon human data. It was also the consensus of the NAC/AEGL to use these data for AEGL-1 and AEGL-2 values. Several LC_{50} data sets from animals were available to derive AEGL-3 values. Following discussion of the various data set elements, the values in the following table were proposed and approved by the NAC/AEGL. The AEGL-1 values were derived from controlled human exposures (Davis, 1934) in which subjects experienced nervousness and slight nausea following 30-minute exposure to 158 ppm. A motion to accept the AEGL-1 values was made by Richard Thomas and seconded by Tom Sobotka. The motion passed unanimously (YES: 24; NO: 0; ABSTAIN: 0; ABSENT: 8). Additional data from Davis supported the AEGL-1 values. Similarly, human data from controlled exposures (Davis, 1934) were used to derive the AEGL-2 values. These were based upon nausea, headache, and vomiting resulting from a 15-minute exposure to 1,191 ppm; one of four subjects found this exposure to be intolerable. A motion to accept the AEGL-2 values was made by Bill Benson and seconded by Bill Bress. The motion passed (YES:18; NO:6; ABSTAIN:0; ABSENT:8). Both the AEGL-1 and AEGL-2 values used a total uncertainty factor of 10 for protection of sensitive individuals (e.g., consumers of alcohol or those exposed to cytochrome P-450 inducers), and temporal extrapolation $C^n \times t = k$, where n = 2.5 based upon animal lethality data. The AEGL-3 values were based upon an estimated lethality threshold (LC_{01}) derived from rat lethality data. A total uncertainty factor of 30 was applied; 10 for protection of sensitive individuals and 3 for interspecies variability (subchronic animal studies showed that long-term exposures at or above the proposed AEGL-3 values did not result in lethal responses). Temporal extrapolation used $C^n \times t = k$, where n = 2.5 based upon animal lethality data. Because there was uncertainty regarding the possibility of delayed hepatotoxic effects, it was suggested that mention be made of antioxidant treatment for exposures to AEGL-2 or AEGL-3 levels. A motion to accept the AEGL-3 values was made by Bill Bress and seconded by Larry Gephart. The motion passed (YES:21; NO:1; ABSTAIN:0; ABSENT:10) (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	16 ppm (100.6 mg/m^3)	12 ppm (75.5 mg/m^3)	6.9 ppm (43.4 mg/m^3)	5.2 ppm (32.7 mg/m^3)	nervousness, slight nausea in human subjects (Davis, 1934)
AEGL-2	90 ppm (566.1 mg/m^3)	68 ppm (427.7 mg/m^3)	39 ppm (245.3 mg/m^3)	30 ppm (188.7 mg/m^3)	nausea, vomiting, headache in human subjects (intolerable to one of four subjects) (Davis, 1934)
AEGL-3	230 ppm (1,446.7 mg/m^3)	170 ppm (1,069.3 mg/m^3)	99 ppm (622.7 mg/m^3)	75 ppm (471.8 mg/m^3)	estimated lethality threshold (LC_{01} = 5,135.5 ppm) in rats (Adams et al.,1952; EPA-OTS, 1986)

Trimethylchlorosilane, CAS No. 75-774
Methyltrichlorosilane, CAS No. 75-79-6

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL

An overview of the information available for these chemicals was presented by Cheryl Bast. Dr. Robert Meeks (representing SEHSC) also provided information regarding current research on some of the chlorosilanes and the difficulties inherent to research on this class of chemicals. Fundamental questions/issues regarding these chemicals include hydrolysis rate and the effect of environmental conditions on the reactivity of these chemicals. Due to the paucity of data on these chemicals and uncertainties regarding the identification of the hydrolysis products and the fate of the silicone moiety, it was the consensus of the NAC/AEGL to defer deliberations pending receipt and incorporation of industry data.

Arsenic Trichloride, CAS No. 7784-34-1

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Robert Young, ORNL

By way of introduction, Bill Bress explained that data pertinent to AEGL derivation were extremely limited for this chemical but that it was being brought before the NAC/AEGL to introduce an elemental equivalent methodology. Robert Young explained that the only data available for the title chemical were unverifiable lethality data from early reports (Attachment 7). These reports lacked experimental details and provided no information on analytical techniques. Although draft proposed AEGL-3 values were provided in the technical support document, Robert Young explained that the data were not considered to be appropriate for derivation of AEGL-3 values for the aforementioned reasons. No additional toxicity data were available for arsenic trichloride and no AEGL-1 values were proposed. Limited data pertinent to AEGL-2, were available for another trivalent arsenical, arsenic trioxide. For AEGL-2, an elemental equivalence approach was introduced whereby an arsenic trichloride exposure is based upon an elemental arsenic equivalence to arsenic trioxide. Robert Young explained that although this approach has been used for Reference Doses, Reference Concentrations and Reportable Quantity values, it did not appear to be scientifically defensible for application to deriving AEGLs for arsenic trichloride. The critical factors driving this judgement included: (1) validity of assuming the arsenic moiety to be the determinant of acute toxicity, (2) differences in physicochemical properties of the two arsenicals, and (3) dramatically different toxic potency of the two arsenicals. It was noted by Robert Young that the decision to recant this approach was attained through discussion among the ORNL staff scientist, the chemical manager, and chemical reviewers (Thomas Hornshaw and Steven Barbee). Although the methodology was considered inappropriate for arsenic trichloride, it is an approach that may be considered in the future where chemical-specific data are unavailable or limited. George Rodgers moved and Ernest Falke seconded that AEGLs not be derived for arsenic trichloride and that an effort be made to determine its inclusion as an AEGL priority chemical. The motion passed unanimously.

Sulfur Dioxide, Sulfur Trioxide, Sulfuric Acid Review

Cheryl Bast presented an overview of currently available data on sulfur dioxide, sulfur trioxide and sulfuric acid.

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

March 10-12, 1998 (at Oak Ridge ??)
June 15-17, 1998
September 14-16, 1998
December 7-9, 1998

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC/AEGL Meeting No. 8 Agenda
2. NAC/AEGL Meeting No. 8 Attendee List
3. Data analysis of Phosgene - Cheryl Bast
4. Data analysis of Phosgene - T.D. Landry
5. Data analysis of Phosgene - Werner Diller
6. Data analysis of Carbontetrachloride - Bob Young
7. Data analysis of Arsenic trichloride - Bob Young

LIST OF APPENDICES

A. Approved NAC/AEGL-7 Meeting Highlights
B. Ballot for Phosgene
C. Ballot for Hydrogen cyanide
D. Ballot for Carbontetrachloride

Attachment 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

DISABLED AMERICAN VETERANS BUILDING
807 Maine Avenue
Washington, D.C. 20024

NAC-8

DRAFT AGENDA

Monday, Dec. 8, 1997

10:00 - 10:15 AM	Introduction and approval of NAC/AEGL-7 highlights (George Rusch)
10:15 - 10:30	Program Director and Designated Federal Officer report (Roger Garrett and Paul Tobin)
10:30 - 12:00	Phosgene (Bill Bress/Cheryl Bast)
12:00 - 1:00 PM	**Lunch**
1:00 - 2:00	Phosgene (Continued)
2:00 - 3:00	Carbon tetrachloride (Bill Bress/Bob Young)
3:00 - 3:15	**Break**
3:15 - 4:45	Carbon tetrachloride (Continued)
4:45 - 5:00	Presentation: Silicones Environmental Health and Safety Council (SEHSC) on Silanes
5:00 - 5:15	Travel reimbursement policy (Paul Tobin/Po-Yung Lu)

Tuesday, Dec. 9, 1997

8:30 - 9:30 AM	SOP Workgroup progress report (Ernie Falke)
9:30 - 10:00	Status Report on Federal Register AEGLs (Paul Tobin)
10:00 - 10:15	**Break**
10:15 - 11:15	Trimethylchlorosilane (Ernie Falke/Cheryl Bast)
11:15 - 12:15 PM	Methyltrichlorosilane (Ernie Falke/Cheryl Bast)
12:15 - 1:15	**Lunch**
1:15 - 3:00	Hydrogen cyanide (George Rodgers/Sylvia Talmage)
3:00 - 3:15	**Break**
3:15 - 3:45	Hydrogen cyanide (Continued)
3:45 - 5:00	Abbreviated ACS presentations: • Rodgers • Kim • Young

Wednesday, Dec10, 1997

8:30 - 10:30 AM	Arsenic trichloride (Bill Bress/Bob Young)
10:30 - 10:45	**Break**
10:45 - 12:00	Brief review of literature of sulfur dioxide, sulfur trioxide, and sulfuric acid (Cheryl Bast)
12:00 - 1:00 PM	Administrative issues
1:00	Adjournment

NAC/AEGL-8

Attachment 2
12/8/97

Name	Affiliation	Phone No.
Po-Yung Lu	ORNL	(423) 574-7803
George Rusch	Allied Signal	973-455-3672
Roger Garrett	EPA	202-260-4302
Kyle Blackman	FEMA	202-646-4676
Jonathan Borak	YCOEM	203-777-6611
Robert Snyder	Rutgers Univ	732-445-3720
Loren Koller	Oregon State University	541-737-5547
Patricia Talcott	U of Idaho	208.885.7081
Bill Bress	@STHO	802-863-7597
Steven J Barbee	Olin Corp/AIHA	203-495-8550 x5435
Bill Pepelko	EPA	202-260-5904
George Rodgers	AAPCC	502-852-8626
Thomas Tuccinardi	DOE-NN61	301 903 2484
Joan Hansen	DOE/BNL	516 344-7535
Thomas J. Sobotka	FDA/CFSAN	301 594-5881
Glenn Leach	Army - CHPPM	410-671-2176
Sylvia Talmage	ORNL	423-576-7758
Cheryl Bast	ORNL	423-574-7581
Robert Young	ORNL	423 574-9888
Mark A. McClanahan	CDC/NCEH	770-488-7297
Jim Holler	ATSDR	404-639-6308
Kenneth R. Still	USNAVY/NAMRI Tox Det	937-255-6054 x202
Lynn M. Beasley	USEPA/Superfund	703 603 9086
Richard D. Thomas	Intercat/ICEH	703-734-1454
Larry Gephart	Exxon	908 873-6319
Leslie Fields	NRC/NMSS	301-415-6267
Nancy Kim	NYS DOH	518 458-6435
George Cushmac	DOT/RSPA	202-366-4493
Ernest Falke	OPPT/EPA	202 260-3433
Bob Benson	EPA Region 8	303-312-7070

NAC/AEGL-8

Name	Affiliation	Phone NO.
Ted Sears	The Technical Group, Inc.	202 962 8562 esears@rcra.com
JOSEPH NIXON	THE TECHNICAL GROUP INC	(202) 962-8548
Alice Lium	Pesticide & Toxic Chem News	410 366-4527 allium@.earthlink.net
Dr. Diller & 2 representatives		
Chris Trent	AMA	703 741 5627
Dr. Lienue DILLER	University Duesseldorf	Germany 0214/47381
TIMOTHY LANDRY	DOW CHEMICAL	517 636 2733 tdlandry@dow.com
Robert Meeks	Dow Corning Corp	517 496 8629 FAX 5595 e-mail rgmeeks@dow.com
Wendy Koch	SEHSC (WITCO)	860 298 6254

Summary of Proposed AEGL Values for Phosgene					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 ppm (2.5 mg/m^3)	0.30 ppm (1.2 mg/m^3)	0.08 ppm (0.33 mg/m^3)	0.04 ppm (0.16 mg/m^3)	Chemical Pneumonia in rats (Gross et al., 1965)
AEGL-3 (Lethality)	1.5 ppm (6.2 mg/m^3)	0.75 ppm (3.1 mg/m^3)	0.20 ppm (0.82 mg/m^3)	0.09 ppm (0.34 mg/m^3)	30-minute No-Effect-Level for death in rats (Zwart et al., 1990)

Attachment 3

HUMAN DATA-

NO EXPOSURE PARAMETERS (CONCENTRATION AND TIME)

IRRITATION:

HEADACHE
DIZZINESS
OCULAR IRRITATION
NAUSEA
VOMITING
IRRITANT COUGH
SICKENING-SWEET TASTE

CLINICAL LATENCY PERIOD: ≤24 HOURS

PULMONARY SYMPTOMS:

COUGH ACCOMPANIED BY EXPECTORATION
SENSATION OF PAIN OR TIGHTNESS OF CHEST
SHORTNESS OF BREATH
CHOKING SENSATION

CLINICAL FINDINGS:

HEMOCONCENTRATION
RALES
PULMONARY EDEMA

The concept of a "death product" was introduced by Haber to explain the relationship between the extent of exposure to phosgene and death (Haber, 1924).

According to "Haber's Law," the biological effect of phosgene is directly proportional to the exposure expressed as the product of the atmospheric concentration (C) and the time of exposure (T) or CT = k, where k can be death, pulmonary edema, or other biological effects of phosgene exposure (US EPA, 1986).

(Use time-specific data rather than extrapolating?)

AEGL-1 FOR PHOSGENE (ppm [mg/m^3])				
AEGL Level	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**NA**	**NA**	**NA**	**NA**

Quantitative data consistent with effects defined by AEGL-1 are not available for phosgene.

It is not appropriate to derive AEGL-1 values for phosgene.

AEGL-2 FOR PHOSGENE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	0.60 [2.5]	0.30 [1.2]	0.08 [0.33]	0.04 [0.16]

Species: Rat
Concentration: 2 ppm phosgene
Time: 1.5 hour
Endpoint: Chemical Pneumonia
Reference: Gross et al., 1965

n = 1

Uncertainty Factor = 10

Interspecies = 3 (little species variability observed for both lethal and non-lethal effects)

Intraspecies = 3 (mechanism is irritation and binding to macromolecules and is not expected to vary greatly between individuals)

Supporting data: Severe pulmonary edema and body weight loss in rats exposed to 1 ppm phosgene for 4 hr (Franch and Hatch, 1986; Erlich et al., 1989). [0.8, 0.4, 0.1, 0.05 ppm]

AEGL-3 FOR PHOSGENE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	1.5 [6.2]	0.75 [3.1]	0.20 [0.82]	0.09 [0.34]

Species: Rat
Concentration: 15 ppm
Time: 30 minutes
Endpoint: No-effect-level for death
Reference: Zwart et al., 1990
n = 1

Uncertainty Factor = 10

Interspecies = 3 (little species variability observed for both lethal and non-lethal effects)

Intraspecies = 3 (mechanism is irritation and binding to macromolecules and is not expected to vary greatly between individuals)

Summary of Proposed AEGL Values for Phosgene					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm	Chemical Pneumonia in rats (Gross et al., 1965)
AEGL-3 (Lethality)	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm	30-minute No-Effect-Level for death in rats (Zwart et al., 1990)

ACGIH TLV (ACGIH, 1991): **0.1 ppm**

NIOSH IDLH (NIOSH, 1994): **2 ppm**

NIOSH STEL (NIOSH, 1994): **0.2 ppm (15 min)**

OSHA PEL (NIOSH, 1994): **0.1 ppm (8 hr)**

ERPG, 1-hour (AIHA, 1989):

ERPG-1: **Not Appropriate**
ERPG-2: **0.2 ppm**
ERPG-3: **1 ppm**

CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

December 5, 1997

Paul S. Tobin, Ph.D.
Designated Federal Officer
National Advisory Committee/AEGL
U.S. Environmental Protection Agency
Mail Stop 7406
401 M. Street
Washington, D.C. 20460

RE: Phosgene AEGL

Dear Dr. Tobin:

This letter is submitted on behalf of the Chemical Manufacturers Association (CMA) Phosgene Panel (Panel) in response to the draft document (NAC/Pro Draft 4: 11/97) proposing Acute Exposure Guideline Levels (AEGL) for phosgene.[1] The Panel supports the efforts of the National Advisory Committee (NAC) in addressing the acute toxicity issues associated with phosgene and appreciates the opportunity to comment on the AEGL document.

Members and representatives of the Panel have reviewed the draft AEGL document and find the proposed values, in general, to be reasonable. However, it is the opinion of the Panel that the values CMA suggested during the September 24, 1997 AEGL Committee meeting were just as reasonable and scientifically justified. (See enclosed table.) The use of Haber's Rule ($c^n t$) in this latest NAC document to extrapolate the 4-hour and 8-hour time points results in proposed AEGL values which are more conservative than necessary.

Despite a contrasting opinion on the issues discussed in the preceding paragraph, the Panel supports the proposed NAC AEGL values because they will help protect the health and safety of the general population. Both the NAC one hour values and the one hour values previously submitted by CMA are similar to the current American Industrial Hygiene Association Emergency Response Planning Guidelines (ERPG), promoting consistency within the industry and government alike.

[1] Members of the Phosgene Panel include: Arco Chemicals Co., BASF Corp., The Dow Chemical Co., DuPont Chambers Works, GE Plastics, PPG Industries, Inc., Rhone-Poulenc Ag. Co., Rubicon, Inc., Van DeMark Chemical Co., Zeneca Ag. Products.

The Panel will be represented at the AEGL Committee meeting on December 8, 1997, by Dr. Timothy Landry, Dow Chemical Company; Ms. Chris Trent, CMA Phosgene Panel Manager; and Professor Dr. med. Werner F. Diller. Professor Diller is an internationally renowned expert in the field of occupational medicine as it relates to phosgene exposure. Professor Diller has reviewed the latest AEGL document and has provided the Panel with his comments. That set of comments is enclosed for your information.

We look forward to meeting with you at the AEGL Committee meeting on December 8, 1997. If you have any questions before then, please contact Chris Trent, Panel Manager, at (703) 741-5627.

Sincerely yours,

Courtney Price /cmt

Courtney M. Price
Vice President, CHEMSTAR

Enclosures

Prof. Dr. med. W. F. Diller
(Consultant: Occupational
and Environmental Health)

Comments on NAC/Pro Draft 4: 11/97

"Acute Exposure Guideline Levels (AEGLs) for Phosgene"

1. General remarks:

The data are well presented, the endpoints well chosen; the proposed values now approach closer the medical experience than the previous draft. Many desirable amendments have been incorporated. However, the proposed values are exclusively based on animal data; due to excessive "uncertainty factors" the proposed values are still significantly too low, when checked for plausibility using experience in humans.

2. Comments on proposed values

AEGL1: The classification "not applicable" is in agreement with the respective ERPG level. Nevertheless, in a case of emergency, authorities as well as the public would be happy to learn that a given exposure is harmless, - e.g. 0,1 ppm for 1 hr (according to the observation by Henschler 1971, and using an UF of 3 for susceptible persons, - and well in agreement with minimal reversible biochemical effects on rat lungs: Currie et al.1978 b; Jaskot et al. 1991).

AEGL 2 + 3: The chosen endpoints agree well with medical experience in humans. The application of an UF of 10 however lowers the proposed values to unrealistically low levels. For example the AEGL 2 (8 hr) proposal ("disabling") of 0,04 is significantly lower than the TLV of 0,1 ppm (which means NOAEL).
The AEGL 3 proposal for 8 hr ("lethality") of 0,09 ppm, is still below the present TLV of 0,1 ppm ("NOAEL").

Of course, one could argue that TLVs are made for working individuals, while AEGLs should be applicable also to susceptible persons. On the other hand, one must keep in mind that work forces, too, comprise individuals with compromised health. Moreover, TLVs are also made for repeated and chronic exposures.
In order to arrive at realistic AEGLs one would have to cut the uncertainty factors. Perhaps one could drop the UF = 3 for interspecies variability, arguing that there is none existing. (Quoting Diller/Zante 1982 with the following interpolations for LCT 50: rat 400, guinea pig 500, man 500, mouse 500). Alternatively one could choose a total UF of 4 (2 for interspecies variability, 2 for susceptible individuals).
Thus, the proposed values could be raised by a factor of 2-3, bringing them to better agreement with medical experience in humans.

3. Minor comments:

p.iii line 8: "none-lethality level in rats" would make more sense than "no-effect level".

p.9 line 10:"teflon smoke" instead of "trflon smoke"

p.10 line 16: continue after "individuals,""while three cases of temporary pulmonary edema were observed at higher exposure levels".

p.15 line 15: Misprint for "sequelae". Insert "after significant acute phosgene exposure..."

p.50 line 14: ACGIH TLV TWA, not ceiling.

Prof. Dr. med. W. Dilier

CMA Phosgene Panel's AEGL proposals

	30 min	1 hour	4 hour	8 hour
AEGL 1	NA	NA	NA	NA
AEGL 2	0.80 ppm	0.27 ppm	0.13 ppm	0.09 ppm
AEGL 3	2.2 ppm	1.1 ppm	0.28 ppm	0.14 ppm

(NA = Not Applicable)

September 19, 1997 12

- 0.09 ppm for 8 hours approximates the TLV.
- 0.14 ppm for 8 hours = 67 ppm.min, this is probably conservative (low) due to the C*t (Haber's rule) extrapolation.
- AIHA ERPG-1 = Not Applicable
  ERPG-2 = 0.2 ppm (one hour)
  ERPG-3 = 1 ppm (one hour)
- The above are appropriate for emergency response preparedness planning.
- Draft AEGL committee proposals (NAC/Pro Draft 3:8/97) are overly conservative based on available animal and human data.
- Consider presentation by Dr. Diller to help assess CMA proposed values.

Diller

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General Comments on Draft 4 (11/97): AEGL's for Phosgene

- Many desirable amendments have been incorporated
- Proposed AEGL's are exclusively based on animal data
- Toxicological endpoints are realistic
- "NA"-classification for AEGL 1 is debatable
- Rigid "uncertainty factors" cause too low proposals for humans

Test for Plausibility of proposed AEGL's for Phosgene

Classification	8 hr AEGL (ppm)	8 hr TLV (ppm)
Level 2: Disabling, irriversible	0,04	0,1
Level 3: Life-threatening	0,09	

LCT_{50} values (ppm min) for small animals and humans *	
rat	400
guinea pig	500
human	500
mouse	500

* Diller-Zante 1982

Derivation of Phosgene AEGL's (ppm) with total UF = 4

Classification	30 min	1 hr	4 hr	8 hr
AEGL 1 (non-disabling)				
AEGL 2 (disabling)	1,5	0,7	0,2	0,1
AEGL 3 (lethality)	3,5	1,7	0,5	0,2

Derivation of Phosgene AEGL's (ppm) with total UF = 3

Classification	30 min	1 hr	4 hr	8 hr
AEGL 1 (non-disabling)				
AEGL 2 (disabling)	2,0	1,0	0,25	0,12
AEGL 3 (lethality)	5,0	2,5	0,6	0,3

Considerations for AEGL 1

Human data relevant to AEGL 1:

0,35 ppm x 1,5 hr (31 ppm min): NOEL for workers (Henschler 1971)

Animal data relevant to AEGL 1:

CT = 30 ppm min: NOEL for pulmonary performance in rats (Rinehart-Hatch 1964)

Resulting proposal for AEGL 1 (UF = 3 for susceptible humans)

0,17 ppm x 1 hr (10 ppm min)

Derivation of Phosgene AEGL's (ppm) with total UF = 3

Classification	30 min	1 hr	4 hr	8 hr
AEGL 1 (non-disabling)	0,3	0,17	0,04	0,02
AEGL 2 (disabling)	2,0	1,0	0,25	0,12
AEGL 3 (lethality)	5,0	2,5	0,6	0,3

CARBON TETRACHLORIDE AEGL PRESENTATION OVERHEADS

NAC/AEGL MEETING NO. 8
December 8-10, 1997
Washington, D.C.

CARBON TETRACHLORIDE
LETHALITY DATA - INHALATION

LC_{LO}

Cat LC_{LO}	38,110 ppm, 2 hrs
Dog LC_{LO}	14,620 ppm, 8 hrs
Guinea pig LC_{LO}	20,000 ppm, 2 hrs
Human LC_{LO}	1,000 ppm, (no duration specified)
Human LC_{LO}	50,000 ppm, 5 min

LC_{50}

Rat LC_{50}	8,000 ppm, 4 hrs
Rat LC_{50}	10,000 ppm, 2 hrs (EPA-OTS, 1986)
Rat LC_{50}	20,000 ppm, 0.25 hrs (EPA-OTS, 1986)
Mouse LC_{50}	9,526 ppm, 8 hrs
"Mammal" LC_{50}	5,486 ppm, (no duration specified)

LC_{01}

Rat LC_{01}	5,153.5 ppm, 1 hr (estimated, AEGL/TSD)

Source: RTECS (1986) unless otherwise noted

EXPOSURE-RESPONSE DATA FOR HUMAN SUBJECTS ACUTELY EXPOSED TO CARBON TETRACHLORIDE

No. of Subjects	Exposure Concentration (ppm) and Time (min)	Response	Reference
6	TWA of 49 ppm (range: 31-87 ppm) for 70 minutes Ct = 57 ppm·hr	odor detection; transient decline in serum iron 20-68 hrs postexposures; elevated urine urobilinogen in one subject; no clinically significant effects and no irritation	Stewart et al. (1961)
6	TWA of 10.9 ppm (range: 10-14.2 ppm) for 180 minutes Ct = 33 ppm·hr	odor detection; no clinically significant effects; no irritation	Stewart et al. (1961)
6	TWA of 10.1 (range: 9-14 ppm) for 180 minutes Ct = 30 ppm·hr	odor detection; no clinically significant effects; no irritation	Stewart et al. (1961)
1	250 ppm (estimated) for 15 minutes Ct = 63 ppm·hr	dizziness and nausea followed by renal failure and death 6 days postexposure (subject was heavy drinker)	Norwood et al. (1951)
2	250 ppm (estimated) for 4 hrs Ct = 1,000 ppm·hr	mild headache and dizziness during exposure (non drinkers)	Norwood et al. (1951)
4	158 ppm for 30 minutes Ct = 79 ppm·hr	nervousness in one subject, no effect in three subjects	Davis, 1934
4	76 ppm for 2 1/2 hours Ct = 190 ppm·hr	no effects	Davis, 1934
4	76 ppm for 4 hours (same subjects as above, 24 hrs later) Ct = 304 ppm·hr	no effects	Davis, 1934
4	317 ppm for 30 minutes Ct = 159 ppm·hr	slight nausea and vomiting, headache	Davis, 1934
4	1,191 ppm for 15 minutes Ct = 298 ppm·hr	nausea, vomiting, headache; intolerable for one subject (9-min exposure only)	Davis, 1934
3	12,800 ppm; 3-7 minutes Ct = 640 ppm·hr	nausea, vomiting, dizziness, listlessness, headache, sleepiness	Davis, 1934
3	12,800 ppm for ≤10 minutes Ct ≤ 2,133 ppm·hr	nausea, vomiting, sleepiness, headache	Davis, 1934
NS	5-117 ppm, 8-hr TWA Ct = 40 - 936 ppm·hr	elevated bilirubin, restricted visual field (imprecise assessments for both)	Smyth et al., 1936

NS: not specified

NONLETHAL EFFECTS OF CARBON TETRACHLORIDE IN LABORATORY SPECIES FOLLOWING INHALATION EXPOSURE

Species	Exposure	Effect	Reference
Rhesus monkey	200 ppm, 8 hrs/day, 5 days/week for 10.5 mos	transient hepatic injury	Smyth et al., 1936
Dog	400 ppm, 7 hrs/day for 6 mos.	decreased body weight	EPA-OTS, 1947
Rat	200 ppm, 8 hrs/day, 5 days/week for 10.5 mos.	no significant effects	Smyth et al., 1936
	50 ppm, 6 hrs	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	250 ppm, 72 min	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	1,000 ppm, 18 min	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	1,000 ppm (six 3-min exposures with 1-hr intervals)	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	63 ppm, 6 hrs/day, 5 days/week for 4 weeks	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	Appelman et al., 1985

NONLETHAL EFFECTS OF CARBON TETRACHLORIDE IN LABORATORY SPECIES FOLLOWING INHALATION EXPOSURE			
	80 ppm 6 hrs/day, 5 days/week for 4 weeks	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	63 ppm (two 3-hr exposures, 1.5 hr intervals)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	80 ppm (two 3-hr exposures, 1.5 hr intervals)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	63 ppm (two 3-hr exposures, 1.5 hr intervals, 5-min peaks of 6-fold baseline)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	80 ppm (two 3-hr exposures, 1.5 hr intervals, 5-min peaks of 6-fold baseline)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	100 ppm, 8 hrs	no significant effect on SDH	Paustenbach et al., 1998b
	100 ppm 11.5 hrs	marginally increased SDH	"
	180 ppm, 15 min	"comatose"; increased ALT at 24 hrs postexposure	Sakata et al., 187
	100 ppm, 2 hrs	no biologically relevant effect	Sanzgiri et al., 1995
	1,000 ppm, 2 hrs	increased ALT and SDH, decreased P-450	"
	50 ppm, 6 hrs	no effect	Wang et al., 1995
	500 ppm, 6 hrs	minor increase in SGOT and	"

NONLETHAL EFFECTS OF CARBON TETRACHLORIDE IN LABORATORY SPECIES FOLLOWING INHALATION EXPOSURE

Species	Exposure	Effect	Reference
Rat	12,000 ppm, 3 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	3,000 ppm, 6 min 3,000 ppm, 9 min	no effect altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	800 ppm, 30 min 800 ppm, 60 min	no effect altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	400 ppm, 60 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	100 ppm, 420 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	50 ppm, 420 min	no effect	Adams et al., 1952
Mouse	8,500 ppm, 0.16 min	ECt_{50} for SGPT activity	Gehring, 1987
	8,500 ppm, 21 min	ECt_{50} for anesthesia	
Rabbit	100 ppm, 2 hrs/week for 23 weeks (increased to 600 ppm by 23 weeks)	increased hexobarbital sleeping time; hepatic fibrosis	Ugazio et al., 1995
Cat	10,000 ppm (via tracheal cannulation) for 15, 30, 60, or 240 minutes	increased total lipids in renal cortex at 15 min; increased relative adrenal wt. ≥15 to 30 min; central necrosis in liver at 240 min	Wong and DiStefano, 1966

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE (CAS NO. 56-23-5)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
6.9 ppm	5.2 ppm	3.0 ppm	2.3 ppm

Reference: Stewart et al., 1961

Test Species/Strain/Number: human volunteers, males, six, 30-59 years old

Exposure Route/Concentrations/Durations: inhalation, TWA of 49 ppm (31-87 ppm) for 72 minutes

Toxicity Endpoint: sweetish, not unpleasant odor; transient reduction in serum iron in two subjects during the first 48 hours after exposure, and an elevated urinary urobilinogen in one subject seven days postexposure

Time Scaling: $C^n \times t = k$, where $n = 2.5$; based on regression analysis of lethality data (Adams et al., 1952)

Concentration/Time Selection/Rationale: TWA of 49 ppm for 70 minutes resulted in odor detection and minor changes in clinical chemistry parameter without signs of toxicity

Uncertainty Factors/Rationale

Total Uncertainty Factor:	10
Interspecies:	none; human subjects
Intraspecies:	10; to account for individual variability in metabolism and disposition of CCl_4

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: none; human subjects

Comments: Derivation of AEGL-1 values using alternate data seta (both human and animal data) resulted in AEGL-1 values ranging from 4-fold less to 2-fold greater than those proposed

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE
(CAS NO. 56-23-5)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
31.7 ppm	24.0 ppm	13.8 ppm	10.5 ppm

Reference: Davis et al., 1934

Test Species/Strain/Number: three human subjects, gender not specified

Exposure Route/Concentrations/Durations: inhalation; 317 ppm for 30 minutes

Toxicity Endpoint: headache, nausea, and vomiting

Time Scaling: $C^n \times t = k$, where $n = 2.5$; based on regression analysis of lethality data (Adams et al., 1952)

Concentration/Time Selection/Rationale: 30-minute exposure to 317 ppm CCl_4 resulted in headache, nausea, and vomiting, but clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure and heart rate) remained normal for up to 48 hours postexposure

Uncertainty Factors/Rationale:

Total Uncertainty Factor:	10
Interspecies:	none; human subjects
Intraspecies:	10; to account for individual variability in metabolism and disposition of CCl_4

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: none; human subjects

Comments: Although not indicative of irreversible effects, the endpoints identified as a basis for the AEGL-2 values are such that ability to egress from the exposure situation may be compromised thereby creating a potential for more serious effects consistent with AEGL-2 definition. AEGL-2 values derived from alternate data sets varied approximately two-fold from the proposed values.

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE (CAS NO. 56-23-5)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
68 ppm	52 ppm	30 ppm	22 ppm

Reference: EPA-OTS, 1946; Adams et al., 1952; EPA-OTS, 1986

Test Species/Strain/Number: Rats/albino or not specified/5-30 per group

Exposure Route/Concentrations/Durations: inhalation/3,000-20,000 ppm/0.1-12 hrs

Toxicity Endpoint: lethality

Time Scaling: $C^n \times t = k$, where $n = 2.5$; based on regression analysis of lethality data from Adams et al. (1952)

Concentration/Time Selection/Rationale: estimated 1-hr LC_{01} (5,153.5 ppm, 1 hr)

Uncertainty Factors/Rationale:

Total Uncertainty Factor:	100
Interspecies:	10 to account for species variability in the metabolism and disposition of carbon tetrachloride
Intraspecies:	10 to account for individual variability in the sensitivity to carbon tetrachloride-induced toxicity (e.g., alcohol-potentiated hepatotoxicity)

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: none

Comments: The proposed AEGL-3 values likely represent a conservative estimate

PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE (ppm [mg/m^3])					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	6.9 [43.4]	5.2 [32.7]	3.0 [18.9]	2.3 [14.5]	Transient, minor increases in serum enzyme activity in human subjects exposed to 49 ppm (TWA) for 70 minutes (Stewart et al., 1961)
AEGL-2	31.7 [199.4]	24.0 [151.0]	13.8 [86.8]	10.5 [66.0]	Nausea, vomiting, headache in human subjects exposed to 317 ppm for 30 minutes (Davis et al. (1934)
AEGL-3	68 [428]	52 [327]	30 [189]	22 [138]	Lethality in rats; estimated LC_{01} (Adams et al., 1952; EPA-OTS, 1986)

SUMMARY OF ALTERNATIVE AEGL DERIVATIONS (ppm)

Endpoint/rational/reference	30 min	1 hr	4 hrs	8 hrs	Comments
AEGL-1					
Stewart et al., 1961; humans; odor detection; minor, transient increase in serum enzymes; 49 ppm (TWA), 70 min; UF=10	6.9	5.2	3.0	2.3	Basis for proposed AEGL-1 values; UF = 10 for intraspecies variability
Stewart et al., 1961; humans; no effect; 10.9 ppm (TWA), 180 min; UF=10	2.2	1.7	0.9	0.7	UF = 10 for intraspecies variability
Davis et al., 1934; humans; no effect; 76 ppm, 2.5 hrs; UF=10	14.5	11.0	6.3	4.8	UF = 10 for intraspecies variability
Paustenbach et al., 1986b; rats; no effect; 100 ppm, 8 hrs; UF=100	3.0	3.0	1.3	1.0	UF = 100; 10 for intraspecies variability, 10 for interspecies variability
Sanzgiri et al., 1995; rats; no effect; 100 ppm, 2 hrs; UF=100	1.7	1.3	0.8	0.6	UF = 100; 10 for intraspecies variability, 10 for interspecies variability
Wang et al., 1995; rats; minor increase in SGPT, SGOT; 500 ppm, 6 hrs; UF=100	13.5	10.2	5.9	4.5	UF = 100; 10 for intraspecies variability, 10 for interspecies variability

SUMMARY OF ALTERNATIVE AEGL DERIVATIONS (ppm)

Endpoint/rational/reference	30 min	1 hr	4 hrs	8 hrs	Comments
AEGL-2					
Davis et al., 1934; humans; nausea, vomiting, headache; 317 ppm, 30 min; UF=10	31.7	24.0	13.8	10.5	Basis for proposed AEGL-2 values; UF = 10 for intraspecies variability
Cornish and Block, 1960; rats; increased SGOT and xanthine oxidase, 1500 ppm, 4 hrs, UF=100[c]	34	26	15	11	UF = 100; 10 for intraspecies variability, 10 for interspecies variability
Davis et al., 1934; human; impaired renal function; 200 ppm, 8 hrs; UF=10	61	46	26	20	UF = 10 for intraspecies variability; anecdotal data
Van Stee et al., 1982; rats; hepatic histopathologic effects; two 1.5 hr exposures to 1500 ppm; exposure interval varied from 1-4 hrs	23.28	17.6	10.13	7.68	UF = 100; 10 for intraspecies variability, 10 for interspecies variability; assumed effect occurred following only one exposure
Wang et al., 1995; rats; minor hepatotoxicity; 500 ppm, 6 hrs; UF=100	13.5	10.2	5.9	4.5	UF = 100; 10 for intraspecies variability, 10 for interspecies variability
Sanzgiri et al., 1995; rats; increased serum enzymes; 1,000 ppm, 2 hrs; UF=100[c]	17.4	13.2	7.6	5.7	UF = 100; 10 for intraspecies variability, 10 for interspecies variability

ISSUES/CONCERNS REGARDING CARBON TETRACHLORIDE AEGLs

- **ANIMAL VERSUS HUMAN DATA**
  - Human data: exposure characterization ?
    identifies sensitive subgroup
  - Animal data: uncertainties inherent in animal data
    necessitate use of UFs that result in potentially overly conservative estimates

- **ARE THE PROPOSED AEGL VALUES OVERLY CONSERVATIVE ?**
  - Alcohol-potentiated hepatotoxicity (a large, potentially very sensitive population)
  - Proposed AEGL-2 indicative of an exposure that could potentially lead to more serious effects; is it overly conservative ?
  - Current AEGL-3 values are below what the data suggest to be far from lethal exposures for humans

ARSENIC TRICHLORIDE AEGL PRESENTATION OVERHEADS

NAC/AEGL MEETING NO. 8
December 8-10, 1997
Washington, D.C.

ARSENIC TRICHLORIDE
AEGL-1

- **Human Data:** **Not available**

- **Animal Data:** **Not available**

- **Toxicity data consistent with AEGL-1 endpoints were unavailable for other arsenicals (e.g., arsenic trioxide)**

ARSENIC TRICHLORIDE
AEGL-2

- **Human Data:** **Not available**

- **Animal Data:** **Not available**

- **Arsenic Trioxide - Nonlethal Toxicity**

  Rats **17 mg/kg (single intratracheal instillation); multifocal interstitial pneumonia, focal proliferative bronchiolitis and alveolitis at 14 days post exposure (Webb et al., 1986)**

  Mice **pregnant mice exposed 4 hrs/day on gestation days 9-12 to 0.26, 2.9, or 28.5 mg/m^3 (0.03, 0.35, 3.42 ppm); exposure-related decrease in fetal body weight, increased incidence of skeletal malformations at highest exposure**

  0.26 mg/m^3 arsenic trioxide produced a significant decrease in fetal body weight

DEVELOPMENTAL TOXICITY IN MICE FOLLOWING INHALATION EXPOSURE OF DAMS TO ARSENIC TRIOXIDE ON GESTATION DAYS 9-12					
Exposure (mg/m^3)	No. of litters	Dead fetuses (%)	Average Fetal wt. (g)	Incidence Retarded growth	Incidence Skeletal malformations
0	8	8	1.272	1/100	2/50
0.26	8	12	1.225*	2/100	3/50
2.9	8	13	1.146*	3/100	7/50
28.5	11	29	0.981*	51/100*	31/50*

* Significantly different from control ($p < 0.05$)
Data from Nagymajtényi et al. (1985)

DERIVATION OF AEGL-2 BY ELEMENTAL EQUIVALENCE TO ARSENIC TRIOXIDE

AEGL-2 FOR ARSENIC TRICHLORIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	0.020 [0.15]	0.014 [0.10]	0.007 [0.05]	0.005 [0.04]

Key study: Nagymajtényi et al. (1985)

Toxicity endpoint: significant decrease in fetal body weight following 4-hr exposures to 0.26 mg As_2O_3/m^3 on gestation days 9-12.

Elemental Equivalence: Adjustment Arsenic trioxide used as surrogate for arsenic trichloride. Arsenic trichloride concentration estimated by elemental equivalence. As_2O_3: 75.74% As; $AsCl_3$: 41.32% As, therefore 0.48 mg $AsCl_3/m^3$ (0.07 ppm) would be required to produce the same amount of As found in 0.26 mg As_2O_3

DERIVATION OF AEGL-2 BY ELEMENTAL EQUIVALENCE TO ARSENIC TRIOXIDE

Scaling: $C^2 \times t = k$ (ten Berge, 1986); midpoint of 2 used in absence of data to empirically derive n.

$$(0.07 \text{ ppm})^2 \times 4 \text{ hrs} = 0.0196 \text{ ppm·hr}$$

(it was assumed that a single 4-hr exposure may have produced the observed effects)

Uncertainty factors: 3 for protection of sensitive individuals; the pregnant animal and the fetus was considered to represent a sensitive population

3 for interspecies variability; mechanism of arsenic toxicity and its target assumed to be similar across species

ARSENIC TRICHLORIDE
AEGL-3

- **Human Data:** **Not available**

- **Animal Data:**

  Cats **20-min LC_{Lo}: 28 ppm (Spector, 1956)**
  1-hr LC_{Lo}: 14 ppm (Flury, 1921)

  Mice **10-min LC_{Lo}: 338 ppm (Flury, 1931)**

- **Available lethality data lack experimental details; verification of data difficult**

ARSENIC TRICHLORIDE
AEGL-3

AEGL-3 FOR ARSENIC TRICHLORIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	0.220 [1.63]	0.156 [1.15]	0.078 [0.58]	0.055 [0.41]

Key study: Flury (1921)

Toxicity endpoint: 1-hr LC_{lo} in cats: 100 mg $AsCl_3$ (14 ppm); experimental details lacking; reduced by 1/3 to estimate lethality threshold: 4.67 ppm

Scaling: $C^2 \times t = k$ (ten Berge, 1986); midpoint of 2 used in absence of data to empirically derive n.

$$(4.67 \text{ ppm})^2 \times 1 \text{ hr} = 21.8 \text{ ppm·hr}$$

Uncertainty factors: 10 for protection of sensitive individuals; data are unavailable regarding individual variability in toxic response or the response of a sensitive population.

3 for interspecies variability; mechanism of arsenic toxicity and its target assumed to be similar across species

ISSUES/CONCERNS REGARDING AEGL VALUES FOR ARSENIC TRICHLORIDE

- **Data consistent with AEGL-1 effects are unavailable**

- **Elemental equivalence (or why elemental equivalence may not be such a great idea)**

  - **extensive assumptions (e.g., arsenic is toxic moiety, mechanism of toxicity similar among arsenicals, metabolism/disposition similar among arsenicals)**

    $$2As_2Cl_3 + 3H_2O \rightarrow As_2O_3 + 6\,HCl$$

    (Is the arsenic moiety relevant in acute exposure situations ???)

  - **differences in physicochemical properties**

ISSUES/CONCERNS REGARDING AEGL VALUES FOR ARSENIC TRICHLORIDE

- **based upon reported lethality values and arsenic content, arsenic trioxide appears to be more potent than the trichloride; it may not be a valid surrogate**

Defaults:

mouse ventilation rate	=	0.06 m^3/kg/hr
mouse body weight	=	0.05 kg
arsenic % in $AsCl_3$	=	41.32%
arsenic % in As_2O_3	=	75.74%

Mouse 10-min LC_{Lo} of 2,500 mg $AsCl_3/m^3$ (Flury, 1931)

Dose (mg As) = [2,500 mg/m^3 x 0.06 m^3/kg/hr x 0.167 hrs x 0.05 kg] x 0.4132

= 0.5 mg As for a 10-min LC_{Lo}

Mouse 3-hr $LC_{>50}$ of 0.94 mg As_2O_3/m^3 (Aranyi et al., 1985)

Dose (mg As) = [0.94 mg/m^3 x 0.06 m^3/kg/hr x 3.0 hrs x 0.05 kg] x 0.7574

= 0.006 mg As for a 3-hr $LC_{>50}$

- **Lethality data are poorly documented and difficult to verify; difficult to verify AEGL-3**

ACUTE EXPOSURE GUIDELINES FOR ARSENIC TRICHLORIDE (CAS NO. 7784-34-1)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not determined	Not determined	Not determined	Not determined

Reference: Pertinent references were unavailable

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Comments: None

ACUTE EXPOSURE GUIDELINES FOR ARSENIC TRICHLORIDE (CAS NO. 7784-34-1)

AEGL-2 VALUES

30 minutes	1 hour	4 hours	8 hours
0.020 ppm	0.014 ppm	0.007 ppm	0.005 ppm

Reference: Nagymajtényi, L. Selypes, A., Berensci, G. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J. Appl. Toxicol. 5: 61-63.

Test Species/Strain/Sex/Number: CFLP mice , 8-11 litters examined

Exposure Route/Concentrations/Durations: inhalation, 0.26, 2.9, 28.5 mg/m^3, 4 hours/day on gestation days 9-12

Effects: exposure related decrease in fetal body weight, increased incidence in skeletal malformations

Exposure (mg/m^3)	Fetal body weight (g)	Retarded growth	Skeletal malformations
0	1.272	1/100	2/50
0.26†	1.225*	2/100	3/50
2.9	1.146*	3/100	7/50
28.5	0.981*	51/100*	31/50*

* Significantly different from controls ($p < 0.05$)
† Determinant for AEGL-2

Endpoint/Concentration/Rationale: The lowest concentration tested (0.26 mg/m^3) resulted in a statistically significant decrease in average fetal body weight.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3; the underlying mechanism of arsenic toxicity (interaction with sulfhydryl groups) is not likely to differ substantially among species
Intraspecies: 3; the fetus was considered to represent a sensitive population
An additional level of conservatism is introduced by the assumption that only one 4-hour exposure resulted in the observed effect
Total uncertainty factor adjustment = 10 (each factor of 3 is considered a logarithmic mean [3.16], therefore 3.16 x 3.16 = 10

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 2; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 1 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of n=2 was used as a default for scaling across time.

Comments: The AEGL-2 values were derived by elemental equivalence using toxicity data from arsenic trioxide. Arsenic trioxide used as surrogate for arsenic trichloride. Arsenic trichloride Adjustment concentration estimated by elemental equivalence to arsenic trioxide. As_2O_3 is 75.74% arsenic; $AsCl_3$ is 41.32% arsenic, therefore 0.48 mg $AsCl_3/m^3$ (0.07 ppm) would be required to produce the same amount of arsenic found in 0.26 mg As_2O_3. Assumptions critical to this approach include: 1) the arsenic moiety is the sole determinant of toxicity, 2) the mechanism of toxicity is similar for trivalent arsenic regardless of the chemical form, and 3) the metabolism and disposition of arsenic trichloride and arsenic trioxide will both yield the arsenic moiety in a similar state of bioavailability. Due to the assumptions and their inherent uncertainties, the confidence in the AEGL-2 values is low.

Because HCl is a hydrolysis product of arsenic trichloride, is use of the arsenic component valid ?

ACUTE EXPOSURE GUIDELINES FOR ARSENIC TRICHLORIDE (CAS NO. 7784-34-1)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.22 ppm	0.16 ppm	0.078 ppm	0.055 ppm

Reference: Flury, F. 1921. Uber kampfgasveriftungen. IX. Lokal reizende arsenverbindungen. Zeichschrift fur die Gesomte. Experimentelle Medizin 13: 527-528.

Test Species/Strain/Sex/Number: cats, sex and number not specified

Exposure Route/Concentrations/Durations: inhalation, tested concentrations not specified

Effects: lethality

Endpoint/Concentration/Rationale: 1-hr LC_{50}

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10; data are unavailable regarding individual variability in the lethal response to arsenic trichloride following inhalation exposure
Intraspecies: 3; the mechanism of arsenic toxicity (interaction with sulfhydryl groups) is expected to be similar among species.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $c^n \times t = k$, where the exponent n ranges from 1 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used as a default for scaling across time.

Comments: Toxicity data for arsenic trichloride is limited to lethality data (LC_{50} and LC_{Lo}) from early reports. These reports provide no information regarding experimental protocol or experimental results. The data are, therefore, not verifiable resulting in AEGL values with very low confidence.

30-min AEGL-2

$C^2 \times 0.5 \text{ hr} = 0.0196 \text{ ppm·hr}$

$C = 0.197 \text{ ppm}$

30-min AEGL-2 = 0.197 ppm/10 = 0.020 ppm (0.15 mg/m^3)

1-hr AEGL-2

$C^2 \times 1 \text{ hr} = 0.0196 \text{ ppm·hr}$

$C = 0.14 \text{ ppm}$

1-hr AEGL-2 = 0.14 ppm/10 = 0.014 ppm (0.10 mg/m^3)

4-hr AEGL-2

$C^2 \times 4 \text{ hrs} = 0.0196 \text{ ppm·hr}$

$C = 0.07 \text{ ppm}$

4-hr AEGL-2 = 0.07 ppm/10 = 0.007 ppm (0.05 mg/m^3)

8-hr AEGL-2

$C^2 \times 8 \text{ hrs} = 0.0196 \text{ ppm·hr}$

$C = 0.05 \text{ ppm}$

8-hr AEGL-2 = 0.05 ppm/10 = 0.005 ppm (0.04 mg/m^3)

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 7 Highlights
Interstate Commerce Commission Building
Hearing Room A
1201 Constitution Avenue, NW
Washington, D.C.
September 23-25, 1997

INTRODUCTION

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 6 (June 9-11, 1997) were reviewed and approved (Appendix A).

Dr. Roger Garrett reported on the AEGL Symposium organized by Drs. Po-Yung Lu, Paul Tobin and Roger Garrett, and held at the American Chemical Society meeting in Las Vegas (September 8-11, 1997). The presentations at the symposium by NAC/AEGL participants were informative and provided a thorough overview of the AEGL process and application. Dr. Falke distributed copies of his presentation regarding his analysis of currently completed AEGL derivations.

Dr. Paul Tobin reported that Federal Register publication of proposed AEGL values for 12 chemicals was expected soon. He also indicated that an internet site is planned for presentation of the Technical Support Documents (TSDs) and relevant information. Paul also reported that Germany was amenable to recognizing AEGLs and emphasized a need for a uniform approach for deriving such values. A WWW address for AEGLs was provided: http://www.epa.gov/fedrgstr. Dr. Tobin indicated that the AEGL information would be under the heading of "Laws and Regulations."

Dr. George Rusch provided a brief overview of the 3rd Occupational Health Assoc. Workshop held in Switzerland this past summer. The considerable attendance at the workshop reflected the high level of interest in harmonization of permissible exposure values. Overall, the approaches used by different groups to derive exposure values did not vary considerably and that scholarly, complete TSDs were key requirements for meaningful and defensible, consistent values.

A question arose regarding the revision cycle for AEGLs. It was suggested that a 7-year revision cycle would probably be appropriate for AEGLs.

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group

Dr. Ernest Falke reported on the progress of the SOP Working Group and provided the NAC/AEGL with work completed thus far. It was evident that notable time and effort had been expended by the Working Group. Specific items discussed by Dr. Falke included drafts of the chemical summary sheets, guidelines for evaluating publications and data for AEGL derivations, and the organizational statement for the SOP

Working Group. Dr. Claudia Troxel will provide a pilot effort in completing the evaluation form for key and supporting studies for propylene oxide. Additional issues of concern, some of which are currently being addressed by the SOP Working Group include: cancer assessments; scientific rationale for uncertainty factor application; use of NOAEL and LOAEL values; nomenclature for AEGLs at their various developmental stages; and format/content of the AEGL TSD. Dr. Rusch commented that sharing the NAC/AEGL SOPs with other agencies and countries would be instrumental in providing credibility to the AEGLs and AEGL process.
Action Item: It was requested that NAC/AEGL members provide written comments to Dr. Falke by October 31, 1997, pertaining to SOP items that were distributed to the NAC/AEGL for comment.

AEGL PRIORITY CHEMICALS

Hydrogen Fluoride, CAS No. 7664-39-3

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Sylvia Talmage, ORNL

Larry Gephart provided an overview of hydrogen fluoride data, a chronology of the hydrogen fluoride AEGL discussions (Attachment 3), and introduced new human exposure data (Lund et al., 1997). Discussion ensued regarding revision of the 10-minute AEGL-2 value and the fact that the Dalbey (1996) data used a very sensitive model (cannulated rat) (Attachment 4). However, following in-depth discussion on revision of the 10-minute AEGL-2 value, the NAC revised the previously proposed 130 ppm value to 95 ppm as the 10-minute AEGL-2. The motion, made by Ernest Falke and seconded by Kyle Blackman, passed [YES:24, NO:0, ABSTAIN:1, ABSENT:9] (Appendix B). The 95 ppm value was based upon a NOAEL. A motion was made by Zarena Post and seconded by Nancy Kim to base AEGL-2 values on 1-hour exposure of dogs and to apply $C^2 \times t = k$ for the 30-minute, 4-hour and 8-hour time periods. Using a total uncertainty factor of 10 (3 for interspecies variability and 3 for intraspecies variability), the resulting AEGL-2 values of 95, 34, 24, 12, and 9 ppm were accepted [YES:23, NO:1, ABSTAIN:1, ABSENT:9] (Appendix C). AEGL-3 values were also revisited (Attachment 5). It was suggested that the uncertainty factor rationale be adjusted such that the interspecies variability UF =1, intraspecies variability UF = 3, and a modifying factor of 2 be applied to account for the steepness of the dose-response curve. The original AEGL-3 values of 170, 62, 44, 22, and 15 ppm were accepted by the NAC during meeting 6 of the NAC/AEGL.
Action item: Incorporate the Lund et al. data in the rationale for AEGL-1 values, noting that it was considered but that it does not impact on the status of the values.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN FLUORIDE						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1, ppm (mg/m^3)	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)	Irritation in humans (Largent, 1960; 1961)
AEGL-2, ppm (mg/m^3)	95 (78)	34 (28)	24 (20)	12 (9.8)	9 (7.4)	NOAEL for lung irritation in cannulated rats (Dalbey, 1996)[a]; Sensory irritation in dogs (Rosenholtz et al., 1963)[b]
AEGL-3, ppm (mg/m^3)	170 (139)	62 (51)	44 (36)	22 (18)	15 (12)	Lung effects in cannulated rats (Dalbey, 1996)[c]; Lethality in mice (Wohlslagel et al., 1976)[d]

[a] 10-minute AEGL-2 value.
[b] 30-minute and 1-, 4-, and 8-hour AEGL-2 values.
[c] 10-minute AEGL-3 value.
[d] 30-minute and 1-, 4-, and 8-hour AEGL-3 values.

Dichlorodimethylsilane, CAS No. 75-78-5

Chemical Manager: Dr. Ernest Falke
Author: Dr. Cheryl Bast, ORNL

There was a brief discussion regarding the relevance of the previously accepted HCl AEGL values and their application to dichlorodimethylsilane. A motion was made (George Rodgers, seconded by William Bress) to accept the proposed new values. The motion passed [YES:21, NO:0, ABSTAIN:3, ABSENT:10] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR DICHLORODIMETHYLSILANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1, ppm (mg/m^3)	0.45 (2.4)	0.45 (2.4)	0.45 (2.4)	0.45 (2.4)	One fourth the HCl AEGL value
AEGL-2, ppm (mg/m^3)	11 (58)	5.5 (29)	1.4 (7.4)	0.68 (3.6)	One fourth the HCl AEGL value
AEGL-3, ppm (mg/m^3)	37 (196)	26 (140)	13 (69)	9 (48)	One-half LC_{50}

Phosgene, CAS No. 75-44-5

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Cheryl Bast, ORNL

William Bress provided a brief introduction followed by an overview of pertinent data and AEGL derivation by Cheryl Bast (Attachment 6). At the request of the Phosgene Panel of the Chemical Manufacturers Association (CMA), Dr. Werner Diller presented information based on his extensive experience with occupational exposure to phosgene (Attachment 7). Dr. Diller discussed pneumonitis and edema as critical effects and noted that pneumonitis is a clinical entity that may not be appropriate as a critical endpoint for deriving AEGL values for phosgene. Dr. Diller provided some information regarding the human experience with phosgene and expressed concerns regarding animal data and its relevance to the human experience. Dr. T.D. Landry (Dow Chemical) also presented an overview of available phosgene data (Attachment 8). Following discussion with Dr. Diller, the NAC/AEGL tabled further deliberations on phosgene pending receipt of written input from Dr. Diller with respect to data that may impact the derivation of AEGL values.

Chloroformates
Methyl chloroformate, CAS No. 79-22-1*
i-Propyl chloroformate, CAS No. 108-23-6**
Propyl chloroformate, CAS No. 109-61-5*

***Chemical Manager: Dr. Ernest Falke, U.S. EPA**
****Chemical Manager: Dr. Doan Hansen, BNL**
Author: Dr. Cheryl Bast, ORNL

Cheryl Bast provided an overview of data for the chloroformates (Attachment 9).

Propyl chloroformate

Data were unavailable for deriving AEGL values for propyl chloroformates. It was suggested that verification of the need for AEGLs for propyl chloroformate and its nomination as an AEGL chemical of concern might be appropriate. It was the consensus of the NAC/AEGL that AEGLs not be derived for propyl chloroformate until additional data and/or justification for its nomination are obtained.

i-Propyl chloroformate

Data were also insufficient for deriving AEGL values for *i*-propyl chloroformate. It was the consensus of the NAC/AEGL that no values be proposed for *i*-propyl chloroformate.

Methyl chloroformate

Following a brief overview of the derivation of the draft AEGL values for methyl chloroformate, there was some discussion regarding the use of data from a subchronic study, histopathology for extrarespiratory tissues and the over all quality of the limited data (Attachment 9). No values were proposed for AEGL-1. A motion (proposed by Loren Koller and seconded by John Hinz) to accept the proposed AEGL-2 and AEGL-3 values did not pass [YES:15, NO:8, ABSTAIN:2, ABSENT:9] (Appendix E). It was decided that a request be made to industry for additional data on this chemical.

Action item: NAC/AEGL members who voted not to accept the proposed values should send their reasons to Cheryl Bast prior to the December 1997 NAC/AEGL meeting.

Propylene Oxide, CAS No. 75-56-9

Chemical Manager: Dr. James Holler, ATSDR
Author: Dr. Claudia Troxel, ORNL

Following introductory statements by James Holler, Claudia Troxel presented a summary of relevant toxicologic data pertaining to the derivation of the draft AEGL values (Attachment 10). Susan Ripple (Dow Chemical), representing the CMA, expressed concerns of the CMA regarding the relevance of AEGL-1 and AEGL-2 endpoints and the magnitude of the uncertainty factor applied for AEGL-3 (Attachment 11). It was the consensus of the NAC/AEGL members that DNA repair was an inappropriate AEGL endpoint. Following discussions, AEGL-3 values were proposed based upon an estimated lethality threshold in mice (859 ppm for 4 hours) and a total uncertainty of 10 (3 for interspecies variability and 3 for intraspecies variability) with an n = 1.2 (based on n derived for ethylene oxide: value of 1.1 in Attachment 11 is incorrect). A motion to accept theses values was proposed by John Hinz and seconded by William Bress. The values were approved [YES:17, NO:4, ABSTAIN:2, ABSENT:11] (Appendix F). AEGL-2 values were based upon dyspnea occurring in mice exposed to 387 ppm for 4 hours (UF = 10: 3 for interspecies, 3 for intraspecies; n = 1.2). The AEGL-2 values were accepted (motion made by Mark McClanahan and seconded by Loren Koller; [YES:17, NO:0, ABSTAIN:4, ABSENT:13] (Appendix F). Vote on a motion proposed by Mark McClanahan and seconded by David Belluck that AEGL-1 values be considered not applicable passed unanimously [YES:20, NO:0, ABSTAIN:1, ABSENT:13] (Appendix F). The proposed draft values are shown in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR PROPYLENE OXIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1, ppm (mg/m^3)	NA	NA	NA	NA	NA
AEGL-2, ppm (mg/m^3)	220 (520)	120 (290)	39 (86)	22 (52)	Dyspnea in mice exposed to 387 ppm for 4 hours (NTP, 1985)
AEGL-3, ppm (mg/m^3)	490 (1200)	270 (640)	86 (200)	48 (110)	Estimated threshold for lethality at 859 ppm for 4 hours (NTP, 1985)

Acrylyl Chloride, CAS No. 814-68-6

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Claudia Troxel, ORNL

Drs. Troxel and McClanahan explained that data were unavailable for derivation of AEGL values for this chemical and that data for SAR approaches were also unavailable (Attachment 12). It was agreed that production volume and distribution data would be examined to determine the need to request studies on acrylyl chloride. A motion to table AEGL derivations and to address issues regarding the need to generate new data was proposed by Loren Koller and seconded by Kyle Blackman. The motion was accepted unanimously by the NAC/AEGL (Appendix G).

Boron Trichloride, CAS No. 10294-34-5

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Claudia Troxel, ORNL

Dr. Claudia Troxel provided an overview of relevant data (Attachment 13). Following discussion regarding the derivation of AEGL values by analogy to hydrogen chloride or the use of boron trichloride-specific data, AEGL-3 values were based upon the Vernot et al. data: 1/3 of the 1-hour LC_{50} value of 2541 ppm in male rats was used for the derivation (847 ppm). A total UF of 30 was applied: 10 for interspecies to account for poor data base and species to species extrapolation and 3 for intraspecies. An n = 1 was used for the temporal scaling. It was noted that these values are consistent with the application of the Stokinger and Spiegl data where exposure to 50 ppm for 2 x 7 hours in rats, mice, and guinea pigs did not result in mortality when clean cages were substituted every 2 hours of the exposure (to reduce contact with the hydrolysis products formed in the cage).

This approach was considered to be consistent to that used for hydrogen chloride and was accepted by the NAC. Because HCl is a hydrolysis product of boron trichloride, the AEGL-1 and AEGL-2 values were derived by a 1/3 reduction of the accepted HCL values and would be considered as guidance values. A motion to accept AEGL-1 and AEGL-2 values was made by Robert Snyder (seconded by Nancy Kin) passed [YES:23, NO:0, ABSTAIN:0, ABSENT:11] (Appendix H). A motion to accept the AEGL-3 draft values was made by George Rodgers and seconded by Tom Sobotka. The motion passed [YES:24, NO:0, ABSTAIN:0, ABSENT:10]. The proposed draft AEGL values are shown in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR BORON TRICHLORIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1, ppm (mg/m^3)	0.60 (2.9)	0.60 (2.9)	0.60 (2.9)	0.60 (2.9)	1/3 the NAC-approved HCl values: recommended as guidance levels
AEGL-2, ppm (mg/m^3)	14 (67)	7.3 (35)	1.8 (8.6)	0.90 (4.3)	1/3 the NAC-approved HCl values: recommended as guidance levels
AEGL-3, ppm (mg/m^3)	57 (270)	28 (130)	7.1 (34)	3.5 (17)	1/3 the 1-hour LC_{50} in male rats (Vernot et al., 1977)

Allyl Alcohol, CAS No. 107-18-6

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Claudia Troxel, ORNL

Dr. Claudia Troxel presented an overview of the data and rationale for derivation of AEGL values (Attachment 14). During initial discussions of the data, it was stated that an individual at Rutgers was conducting research on the metabolism and toxicity of allyl alcohol and that data from such studies may be useful in assessments for this chemical. Following discussions of various approaches for setting AEGL-3 values, a set of values based upon a 1-hr LC_{50} (value adjusted for 25% loss of chemical during exposure) in

rats (UF = 10, n = 2) was unanimously accepted (motion by John Hinz, seconded by William Pepelko; [YES:21, NO:1, ABSTAIN:0, ABSENT:12] (Appendix I). It was noted that the AEGL-3 values were supported by the NOEL for death of 200 ppm for 1 hour in rats, mice, and rabbits. A motion was made by Robert Snyder and seconded by Loren Koller to accept the AEGL-2 values as originally proposed by Drs. Troxel and McClanahan. The motion was passed [YES:18, NO:4, ABSTAIN:0, ABSENT:12] (Appendix I). It was noted that the values are supported by a 60 ppm exposure for 7 hours. The AEGL-1 values as originally proposed were also accepted (motion by William Bress, seconded by Zarena Post; [YES:18, NO:4, ABSTAIN:0, ABSENT:12]) (Appendix I). The proposed draft values are summarized in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR ALLYL ALCOHOL					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1, ppm (mg/m^3)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	Mean odor detection threshold (AIHA, 1989)
AEGL-2, ppm (mg/m^3)	15 (36)	11 (26)	5.3 (13)	3.7 (9.0)	Exposure to 40 ppm for 7 hr/d caused irritation during the first few exposures (Dunlap et al., 1958)
AEGL-3, ppm (mg/m^3)	35 (85)	25 (61)	13 (31)	8.8 (21)	1/3 of the 1-hour LC_{50} in rats (the 1-hour LC50 value adjusted for 25% loss of chemical during exposure) (Dunlap et al., 1958)

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

NAC-8, December 8-10, 1997,Washington, DC
NAC-9, March 10-12, 1998, Oak Ridge, TN
NAC-10, June 15-17, 1998, Washington, DC
NAC-11, September 15-17, 1998, Washington, DC

Draft highlights of NAC-7 were prepared by Drs. R. A. Young and P. Y. Lu of ORNL.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC Meeting No. 7 Agenda
2. NAC Meeting No. 7 Attendee List
3. Overview of Hydrogen fluoride - Larry Gephart
4. Data analysis of Hydrogen fluoride - Larry Gephart
5. Additional data analysis of hydrogen fluoride - Sylvia Talmage and Larry Gephart
6. Data analysis of Phosgene - Cheryl Bast
7. Data analysis of Phosgene - Werner Diller
8. Data analysis of Phosgene - T.D. Landry
9. Data analysis of Chloroformates - Cheryl Bast
10. Data analysis of Propylene oxide - Claudia Troxel
11. Additional data analysis of Propylene oxide from Courtney M. Price, CMA
12. Data analysis of Acrylyl chloride - Claudia Troxel
13. Data analysis of Boron trichloride - Claudia Troxel
14. Data analysis of Allyl alcohol - Claudia Troxel
16. Data analysis of TDI data - Carol Forsyth
17. Data analysis of derivation of AEGLs for Aniline - Sylvia Talmage
18. Introduction of isopropyl chloroformate - Doan Hansen
19. Data summaries of isopropyl chloroformate and Methyl and Propyl chloroformate - Cheryl Bast

LIST OF APPENDICES

A. Approved NAC-6 Meeting Highlights
B. Ballot for Hydrogen fluoride
C. Ballot for Hydrogen fluoride
D. Ballot for Dichlorodimethylsilane
E. Ballot for Methyl chloroformate
F. Ballot for Propylene oxide
G. Ballot for Acrylyl chloride
H. Ballot for Boron trichloride
I. Ballot for Allyl alcohol

75-44-5

Appendix B

Date of AEGL NAC meeting: **Chemical:** Phosgene

NAC Member	AEGL1	AEGL2	AEGL3	NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff	A			Nancy K. Kim	Y		
Steven Barbee	Y			Loren Koller	Y		
Lynn Beasley	Y			Glenn Leach	Y		
David Belluck	A			Mark A. McClanahan	Y		
Robert Benson	Y			John S. Morawetz	A		
Kyle Blackman	Y			Richard W. Niemeier	A		
Jonathan Borak	Y			William Pepelko	Y		
William Bress	Y			Zarena Post	A		
Luz Claudio	A			George Rodgers	Y		
Guy Colonna	A			George Rusch, Chair	Y		
George Cushmac	Y			Bob Snyder	Y		
Ernest Falke	Y			Thomas J. Sobotka	Y		
Larry Gephart	Y			Kenneth Still	Y		
John Hinz	A			Patricia Ann Talcott	Y		
Jim Holler	Y			Richard Thomas	Y		
Thomas C. Hornshaw	A			Thomas Tuccinardi/ Doan Hansen	Y/Y		
				TALLY	23/23		

A: Absent 0 ; Y: Yes 23 ; N: No 0.

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	0,6 ,( )	0,3 ,( )	0,08 ,( )	0,04 ,( )
AEGL 3	1,5 ,( )	0,75 ,( )	0,20 ,( )	0,09 ,( )

AEGL 1 Motion: Koller **Second:** Rodgers

AEGL 2 Motion: " **Second:** "

AEGL 3 Motion: " **Second:** "

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 12-8-97

Comments:

56-23-5

Appendix D

Date of AEGL NAC meeting: **Chemical:** Carbon tetrachloride CCl4

NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	A	A	A
Robert Benson	Y	Y	N
Kyle Blackman	Y	Y	Y
Jonathan Borak	A	A	Y
William Bress	Y	Y	Y
Luz Claudio	A	A	A
Guy Colonna	A	A	A
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	A	A	A
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	A	A	A

NAC Member	AEGL1	AEGL2	AEGL3
Nancy K. Kim	Y	Y	Y
Loren Koller	Y	Y	Y
Glenn Leach	Y	N	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	N	A
Richard W. Niemeier	Y	N	A
William Pepelko	Y	N	Y
Zarena Post	A	A	A
George Rodgers	Y	N	Y
George Rusch, Chair	Y	Y	Y
Bob Snyder	Y	N	Y
Thomas J. Sobotka	Y	Y	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Y	Y	Y
Richard Thomas	Y	Y	A
Thomas Tuccinardi/ Doan Hansen	Y / Y	Y / Y	Y / Y
TALLY	0/24	6/18	1/21

A: Absent ; Y: yes ; N: no.

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	16 ~~32~~ ,( )	12 ~~24~~ ,( )	6 ~~9~~ ~~4~~ ,( )	5.2 ~~10~~ ,( )
AEGL 2	90 ,( )	65 ,( )	39 ,( )	30 ,( )
AEGL 3	230 ,( )	170 ,( )	99 ,( )	75 ,( )

AEGL 1 Motion: Richard Thomas ~~Bob Benson~~ **Second:** Tom Sobotka ~~Mark McClanahan~~ n=2.5; UF=10

AEGL 2 Motion: Bob Benson **Second:** Bill Bress n=2.5; UF=10

AEGL 3 Motion: Bill Bress **Second:** ~~Larry Gephart~~ n=2.5; UF=30 (10x3)

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12.4.97

Comments:

74-90-8

Appendix C

Date of AEGL NAC meeting: 12-7-97 Chemical: HCN

NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	A	A	A
Robert Benson	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
Luz Claudio	A	A	A
Guy Colonna	A	A	A
George Cushnac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	A	A	A
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y

NAC Member	AEGL1	AEGL2	AEGL3
Nancy K. Kim	Y	Y	Y
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	Y	Y	Y
George Rusch, Chair	Y	Y	Y
Bob Snyder	N	N	N
Thomas J. Sobotka	A	A	A
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Y	Y	Y
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	Y Y	Y Y	Y Y
TALLY	23		

A = Absent 8; Y = Yes 23 ; N = No - 1

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	10 ,( )	7.1 ,( )	3.5 ,( )	2.6 ,( )
AEGL 3	21 ,( )	15 ,( )	8.6 ,( )	6.6 ,( )

AEGL 1 Motion: Rogers Second: Koller

AEGL 2 Motion: " Second: " Intra UF=1 Inter UF=3 MF = 2

AEGL 3 Motion: " Second: " "

Approved by Chair: [signature] DFO: Paul S. Date: 12-9-97

Comments: